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DRAFT

DIURON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

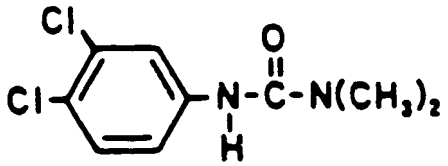
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 330-54-1

Structural Formula



N'-(3,4-Dichlorophenyl)-N,N-dimethylurea

Synonyms

- Crisuron; Dailon; Di-on; Dichlorfendism; Diurex, Drexel; Duran; Dynex; DCMU; Herbatox; HW 920; Karmex; Sup'r flo; Telvar, Urox D; Vonduron (Meister, 1983).

Uses

- Pre-emergence herbicide (Meister, 1984).

Properties (Meister, 1984; Windholz et al., 1983)

Chemical Formula	$C_9H_{10}N_2OCl_2$
Molecular Weight	233.10
Physical State (at 25°C)	White crystalline solid
Boiling Point	--
Melting Point	158-159°C
Vapor Pressure (20°C)	3.1×10^{-6} mm Hg
Specific Gravity	--
Water Solubility (25°C)	42 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Diuron has been found in none of the 8 surface water samples analyzed and in 25 of 939 ground water samples (STORET, 1987). Samples were collected at 6 surface water locations and 930 ground water locations, and diuron was found only in California and Georgia. The 85th percentile of all non-zero samples was 1 ug/L in ground water sources only. The maximum concentration found in ground water was 5 ug/L.

- Diuron residues as a result of agricultural practice have been detected in ground waters in California in wells at low (e.g., 2 to 3 ppb) levels (California Department of Food and Agriculture, 1986).

Environmental Fate

- Radiolabeled diuron and its degradation products 3-(3,4-dichlorophenyl)-1-methylurea (DCPMU) and 3-(3,4-dichlorophenyl)urea (DCPU) had half-lives of 4 to 8, 5, and 1 month, respectively, in aerobic soils maintained at 18 to 29°C and moisture levels at approximately field capacity (Walker and Roberts, 1978; Elder, 1978). 3,4-Dichloroaniline (DCA) was identified as a minor degradation product of diuron (Belasco, 1967; Belasco and Pease, 1969; Elder, 1978). Increasing soil organic matter content appears to increase the rate of decline of diuron phytotoxic residues (McCormick, 1965; Corbin and Upchurch, 1967; McCormick and Hiltbold, 1966; Liu et al., 1970).

- Degradation of diuron phytotoxic residues is much (28 to 50%) slower in flooded soil than in aerobic soil (Imamliev and Bersonova, 1969; Wang et al., 1977).

- Diuron has a low-to-intermediate mobility in fine to coarse-textured soils and freshwater sediments (Hance 1965a; Hance, 1965b; Harris and Sheets, 1965; Harris, 1967; Helling and Turner, 1968; Grover and Hance, 1969; Gerber et al., 1971; Green and Corey, 1971; Helling, 1971; Guth, 1972; Grover, 1975; Helling, 1975). Mobility is correlated with organic matter content and (CEC). Soil texture apparently is not, by itself, a major factor governing the mobility of diuron in soil.

- In a study using radiolabeled material, the diuron degradation products (96% pure) had K_d values of 66 and 115 in silty clay loam soils, indicating that they are relatively immobile or less mobile than diuron (Elder, 1978).

- In the field, diuron residues (nonspecific method used) generally persisted for up to 12 months in soils that ranged in texture from sand to silt loam treated with diuron at 0.8 to 4 lb/A (Cowart, 1954; Hill et al., 1955; Weed et al., 1953; Weed et al., 1954; Miller et al., 1978). These residues may leach in soil to a depth of 120 cm (4 feet). Diuron was detectable (3 to 74 ppb) in runoff-water sediment and soil samples for up to 3 years after the last application to pineapple-sugarcane fields in Hawaii (Mukhtar, 1976; Green et al., 1977).

- Phytotoxic residues persisted for up to 12 months in soils ranging in texture from sand to silty clay loam to boggy meadow soil following the last of one to six annual applications of diuron at 1 to 18 lb/A (Weldon and Timmons, 1961; Dalton et al., 1965; Bowmer, 1972; Dawson et al., 1978; Arle et al., 1965; Wang and Tsay, 1974; Spiridonov et al., 1972; Addison and Bardsley, 1968; Cowart, 1954; Hill et al., 1955; Weed et al, 1953; Weed et al., 1954). Diuron persistence in soil appears to be a function of application rate and amount of rainfall and/or irrigation water. Three degradation products (DCPMU, DCPU, and DCA) were identified in soil (planted to cotton) that had received multiple applications of diuron (80% wettable powder totaling 5 to 5.7 lb/A (Dalton et al., 1965).

- Diuron persists in irrigation-canal soils for 6 or more months following application at 33 to 46 kg/ha (Evans and Duseja, 1973a; Evans and

Duseja, 1973b; Bowmer and Adeney, 1978a; Bowmer and Adeney, 1978b). The relative percentages of diuron and its degradates DCPMU and DCPU were 60-90:10-25:1-30 in clay and sandy clay soils, 4.5 to 17 weeks after treatment. Diuron levels in water samples were highest (0.5 to 8 ppm) in the initial flush of irrigation water. These levels declined rapidly, probably as a function of dilution and not degradation.

III. PHARMACOKINETICS

Absorption

° Diuron is absorbed through the gastrointestinal tract of rats and dogs. Hodge et al. (1967) fed diuron to rats and dogs at dietary levels from 25 to 2,500 ppm and from 25 to 1,250 ppm active ingredient (a.i.), respectively, for periods up to two years. These doses are equivalent to 1.25 to 125 mg/kg/day for the rat and 0.635 to 31.25 mg/kg/day for the dog. Urinary and fecal excretion products after one week to 2 years accounted for about 10% of the daily dose ingested. The excretion data provided evidence that gastrointestinal absorption ocurred in rats and dogs.

Distribution

° Hodge et al. (1967) fed diuron (80% wettable powder) for 2 years to rats at dietary levels of 25 to 2,500 ppm a.i. and to dogs at dietary levels of 25 to 1,250 ppm a.i. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day in rats and 0.025 mg/kg/day in dogs, this corresponds to doses of 1.25 to 125 mg/kg/day in rats and 0.625 to 31.25 mg/kg/day in dogs (Lehman, 1959). Analysis of tissue samples for diuron residues revealed levels ranging from 0.2 to 56 ppm, depending on dose. This constituted only a minute fraction of the total dose ingested. The authors concluded that there was little diuron storage in tissues.

Metabolism

° Geldmacher von Mallinckrodt and Schlussier (1971) analyzed the urine of a woman who had ingested a dose of 38 mg/kg of diuron along with 20 mg/kg of aminotriazole. The urine was found to contain 1-(3,4-dichlorophenyl)-3-methylurea and 1-(3,4-dichlorophenyl)-urea, and may also have contained some 3,4-dichloroaniline. No unaltered diuron was detected.

° Hodge et al. (1967) fed diuron (80% wettable powder) to male beagle dogs at a dietary level of 125 ppm active ingredient for 2 years. Assuming that 1 ppm in the diet is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to a dose of 3.1 mg/kg/day. Analysis of urine at weeks one to four or after two years revealed the major metabolite was N-(3,4-dichlorophenyl)-urea. Small amounts of

N-(3,4-dichlorophenyl)-N'-methylurea, 3,4-dichloroanaline, 3,4-dichlorophenol and unmetabolized diuron also were detected.

Excretion

- Hodge et al. (1967) fed diuron (80% wettable powder) for 2 years to rats at dietary levels of 25 to 2,500 ppm and to dogs at dietary levels of 25 to 1,250 ppm. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day in rats and 0.025 mg/kg/day in dogs, this corresponds to doses of 1.25 to 125 mg/kg/day in rats and 0.625 to 31.25 mg/kg/day in dogs (Lehman, 1959). In rats, urinary excretion (6.3 to 492 ppm, depending on dose) was consistently greater than fecal excretion (1.0 to 204 ppm). In dogs, urinary excretion (6.3 to 307 ppm) was similar to fecal excretion (7.9 to 308 ppm). For both rats and dogs, combined urinary and fecal excretion accounted for only about 10% of the daily diuron ingestion.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of diuron in humans.

Animals

Short-term Exposure

- Acute oral LD_{50} values of 1,017 mg/kg and 3,750 mg/kg have been reported in albino rats by Boyd and Krupa (1970), NIOSH (1985) and Taylor (1976a), respectively. Signs of central nervous system depression were noted after treatment.

- Hodge et al. (1967) administered single oral doses of recrystallized diuron in peanut oil to male CR rats. The approximate lethal dose was 5,000 mg/kg, and the LD_{50} was 3,400 mg/kg. Survivors sacrificed after 14 days showed large and dark-colored spleens with numerous foci of blood formation.

- Hodge et al. (1967) administered oral doses of 1,000 mg/kg of recrystallized diuron five times a week for 2 weeks (10 doses) to six male CR rats. At necropsy, 3 or 11 days after the final dose, the spleens were large, dark and congested, and foci of blood formations were noted in both the spleen and bone marrow.

- Hodge et al. (1967) fed Wistar rats (five/sex/dose) diuron (purity not specified) in the diet for 42 days at dose levels of 0, 200, 400, 2,000, 4,000 or 8,000 ppm a.i. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 10, 20, 100, 200 or 400 mg/kg/day. Following treatment body weight, clinical chemistry, food consumption, hematology, urinalysis and histology were evaluated. No effects were observed at

400 ppm (20 mg/kg/day) or less. At 2,000 ppm (100 mg/kg/day) or greater, red blood cell counts and hemoglobin values were decreased. A marked inhibition of growth occurred in the 4,000 ppm (200 mg/kg/day) or greater dosage groups, and there was increased mortality at 8,000 ppm. Based on these data, a No-Observed-Adverse-Effect-Level (NOAEL) of 400 ppm (20 mg/kg/day) and a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 2,000 ppm (100 mg/kg/day) were identified.

Dermal/Ocular Effects

- Taylor (1976b) applied diuron (98% pure) to the intact or abraded skin of eight albino rabbits at dose levels of 1,000 to 2,500 mg/kg for 24 hours. After treatment, a slight erythema was observed, but no other symptoms of toxicity were noted during a 14-day observation period. The dermal LD_{50} was reported as >2,500 mg/kg.

- Larson (1976) applied diuron (98% pure) at doses of 1, 2.5, 5 or 10 mg/kg to intact abraded skin of rabbits for 24 hours. Adverse effects were not detected in exposed animals.

- In studies conducted by DuPont (no date), diuron (50% water paste) was not irritating to intact skin and was moderately irritating to abraded skin of guinea pigs. No data were available on skin sensitization. See also DuPont (1961).

- In studies conducted by Larson and Schaefer (1976), 10 mg of a fine dry powder of diuron (98% a.i.) was instilled into the conjunctival sac of one eye of each of six New Zealand White rabbits. Ocular irritation was not detected within 72 hours.

Long-term Exposure

- Hodge et al. (1967) fed albino Charles River rats (five/sex/dose) diuron (98% pure) for 90 days at dietary levels of 0, 50, 500 or 5,000 ppm. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 2.5, 25 or 250 mg/kg/day. Following treatment, body weight, food consumption, clinical chemistry and histopathology were evaluated. No adverse effects were observed in any parameter at 50 ppm. At 500 ppm there were no effects on males, but females gained less weight than controls and appeared cyanotic. At the 5,000-ppm dose level, body weights were reduced in both sexes, spleens were enlarged and exhibited hemosiderosis, and there was clinical and pathological evidence of chronic methemoglobinemia. Based on these data, a NOAEL of 50 ppm (2.5 mg/kg/day) and a LOAEL of 500 ppm (25 mg/kg/day) were identified.

- Hodge et al. (1967) fed diuron (80% wettable powder) to groups of Charles River rats (20/sex/dose) for 90 days at dietary levels of 0, 250 or 2,500 ppm active ingredient. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 12.5 or 125 mg/kg/day. At 2,500 ppm, both males and females ate less and gained less weight did than controls. There was a slight decrease in red blood cell count, greater in females than in

males. No effect on food consumption or weight gain was noted at 250 ppm, but hematological changes were evident in females. This study identified a LOAEL of 250 ppm (12.5 mg/kg/day), the lowest dose tested.

- In a 2-year feeding study conducted by Hodge et al. (1964a, 1967), beagle dogs (two males/dose and three females/dose) were administered technical diuron (80% a.i.) in the diet at dose levels of 0, 25, 125, 250 or 1,250 ppm active ingredient. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of diuron of 0, 0.625, 3.12, 6.25 or 31.25 mg/kg/day. Following treatment, body weight, clinical chemistry, hematology, organ weight, gross pathology and histopathology were evaluated. No adverse effects were reported at 25 ppm in any parameter measured. Abnormal blood pigment was observed at 125 ppm or greater. Hematological alterations (depressed red blood cells (RBC), hematocrit and hemoglobin) were observed at 250 ppm or greater. In the 1,250 ppm group, a slight weight loss occurred as well as increased erythrogenic activity in bone marrow and hemosiderosis of the spleen. Based on these data, a NOAEL of 25 ppm (0.625 mg/kg/day) and a LOAEL of 125 ppm (3.12 mg/kg/day) were identified.

- Hodge et al. (1964b, 1967) administered technical diuron (80% a.i.) in the diet of rats (35/sex/dose) for 2 years at dose levels of 0, 25, 125, 250 or 2,500 ppm active ingredient. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of diuron of 0, 1.25, 6.25, 12.5 or 125 mg/kg/day. Following treatment, body weight, clinical chemistry, hematology, food consumption, urinalysis, organ weights and histopathology were evaluated. No adverse effects were reported at 25 ppm (1.25 mg/kg/day) for any parameters measured. Abnormal blood pigments (sulfhemoglobin) were observed at 125 ppm (6.25 mg/kg/day) or greater. Hematological changes (decreased RBC, reduced hemoglobin), growth depression, hemosiderosis of the spleen and increased mortality were observed at 250 ppm (12.5 mg/kg/day) or greater. Based on these data, a NOAEL of 25 ppm (1.25 mg/kg/day) and a LOAEL of 125 ppm (6.25 mg/kg/day) were identified.

Reproductive Effects

- Hodge et al. (1964b, 1967) studied the effects of diuron (80% wettable powder) in a three-generation reproduction study in rats. Animals were supplied food containing 125 ppm active ingredient. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to a dose of 6.25 mg/kg/day. Fertility rate, body weight, hematology and histopathology were monitored. No effect was seen on any parameter except body weight, which significantly decreased in the F_{2b} and F_{3a} litters. A LOAEL of 125 ppm (6.25 mg/kg/day) was identified.

Developmental Effects

- Khera et al. (1979) administered by gavage a formulation containing 80% diuron at dose levels of 125, 250 or 500 mg/kg of formulation to

pregnant Wistar rats (14 to 18/dose) on days 6 through 15 of gestation. Vehicle (corn oil) controls (19 dams) were run concurrently. No maternal or teratogenic effects were observed at 125 mg/kg/day. Developmental effects appeared to increase in all treatment groups, i.e. wavy ribs, extra ribs and delayed ossification. The incidence of wavy ribs was statistically significant at 250 mg/kg and greater. Maternal and fetal body weights decreased significantly at 500 mg/kg ($p < 0.05$). A NOAEL was not determined from this study for fetotoxic effects; hence, a LOAEL of 125 mg/kg of formulation per day was identified.

Mutagenicity

- Andersen et al. (1972) reported that diuron did not exhibit mutagenic activity in T_4 bacteriophage test systems (100 ug/plate) or in tests with eight histidine-requiring mutants of Salmonella typhimurium (small crystals applied directly to surface of plate).

- Fahrig (1974) reported that diuron (purity not specified) was not mutagenic in a liquid holding test for mitotic gene conversion in Saccharomyces cerevisiae, in a liquid holding test for forward mutation to streptomycin resistance in Escherichia coli, in a spot test for back mutation in S. marcescens or in a spot test for forward mutation in E. coli.

- Recent studies by DuPont (1985) did not detect evidence of mutagenic activity for diuron in reversion tests in several strains of S. typhimurium (with or without metabolic activation), in a Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward gene mutation test or in unscheduled DNA synthesis tests in primary rat hepatocytes. However, in an in vivo cytogenetic test in rats, diuron was observed to cause clastogenic effects.

Carcinogenicity

- Hodge et al. (1964b, 1967) fed Wistar rats (35/sex/dose) diuron (80% wettable powder) in the diet at levels of 0, 25, 125, 250 or 2,500 ppm a.i. for 2 years. Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 1.25, 12.5 or 125 mg/kg/day. There was some early mortality in males at 250 and 2,500 ppm, but the authors ascribed this to viral infection. Histological examination of tissues showed no evidence of changes related to diuron; however, only 10 animals or fewer were examined per group. Tumors and neoplastic changes observed were similar in exposed and control groups, and the authors concluded there was no evidence that diuron was carcinogenic in rats.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data

are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for use in the determination of the One-day HA value for diuron. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, calculated below as 1.0 mg/L (1,000 ug/L) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Khera et al. (1979) has been selected to serve as the basis for the Ten-day HA for diuron. In this study, pregnant rats were administered diuron (80%) on days 6 through 15 of gestation at dose levels of 125, 250 or 500 mg/kg/day. Developmental effects appeared to increase in the diuron-treated groups as compared to the control group, i.e. wavy ribs, extra ribs and delayed ossification. The incidence of wavy ribs was statistically significant at 250 mg/kg/day ($p < 0.05$). Fetal and maternal body weights were decreased at 500 mg/kg ($p < 0.05$). A NOAEL was not determined from this study at the lowest dose tested (LDT) based on developmental toxicity; hence, the LOAEL for this study was 125 mg/kg/day (LDT).

Using a LOAEL of 125 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-Day HA} = \frac{(125 \text{ mg/kg/day}) (10 \text{ kg}) (0.80)}{(1{,}000) (1 \text{ L/day})} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

125 mg/kg/day = LOAEL, based on fetotoxicity in rats exposed to diuron via the diet for days 6 through 15 of gestation.

10 kg = assumed body weight of a child.

0.80 = correction factor to account for 80% active ingredient.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day feeding study in rats by Hodge et al. (1967) has been chosen to serve as the basis for determination of the Longer-term HA values for diuron. In this study, five animals per sex were fed diuron (98% pure) at dose levels of 0, 2.5, 25 or 250 mg/kg/day. Based on decreased weight gain and methemoglobinemia, this study identified a NOAEL of 2.5 mg/kg/day and a LOAEL of 25 mg/kg/day. These values are supported by the 42-day feeding study of Hodge et al. (1964b), in which a NOAEL of 20 mg/kg/day and a LOAEL of 100 mg/kg/day were identified. This study was not selected, however, since the duration of exposure was only 42 days.

Using a NOAEL of 2.5 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.25 \text{ mg/L } (250 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of effects on weight gain or blood chemistry in rats exposed to diuron via the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.875 \text{ mg/L } (875 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of effects on weight gain or blood chemistry in rats exposed to diuron via the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in dogs by Hodge et al. (1964a, 1967) has been selected to serve as the basis for the Lifetime HA for diuron. In this study, dogs (three/sex/dose) were fed diuron at doses of 0.625, 3.12, 6.25 or 31.15 mg/kg/day of active ingredient. Hematological alterations were observed at 3.12 mg/kg/day or greater, and this was identified as the LOAEL. No effects were reported at 0.625 mg/kg/day in any parameter measured, and this was identified as the NOAEL. This value is supported by a lifetime study in rats by the same authors (Hodge et al., 1964b). In this study, rats were fed diuron at dose levels of 0, 1.25, 6.25, 12.5 or 125 mg/kg/day for 2 years. Hematological changes were observed at 6.25 mg/kg/day or greater, and a NOAEL of 1.25 mg/kg/day was identified.

Using a NOAEL of 0.625 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.625 \text{ mg/kg/day})}{(100)\ (3)} = 0.002 \text{ mg/kg/day}$$

where:

0.625 mg/kg/day = NOAEL, based on absence of hematological effects in dogs exposed to diuron via the diet for 2 years.

100 = uncertainty factor chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = additional uncertainty factor used in the Office of Pesticide Programs (U.S. EPA, 1987). This factor is used to account for a lack of adequate chronic toxicity studies in the data base preventing establishment of the most sensitive toxicological end point.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.002 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.07 \text{ mg/L } (70 \text{ ug/L})$$

where:

0.002 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.07 mg/L) (20%) = 0.014 mg/L (14 ug/L)

where:

0.07 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Hodge et al. (1964b, 1967) fed rats (35/sex/dose) diuron in the diet at ingested doses of up to 125 mg/kg/day for 2 years. Histological examinations did not reveal increased frequency of tumors; however, fewer than half of the survivors were examined.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of diuron.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), diuron may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

- Structurally related analogue(s) (e.g., linuron) of diuron appears to reflect some oncogenic activity. In addition, a Russian study by Rubenchik et. al. (1973) reported gastric carcinomas and pancreatic adenomas in rats (strain not designated) given 450 mg/kg/ day for

22 months. However, the actual data for the study is unavailable for Agency review.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- An Acceptable Daily Intake (ADI) of 0.002 mg/kg/day, based on a NOAEL of 0.625 mg/kg from a dog study and an uncertainty factor of 300 has been calculated (U.S. EPA, 1986b).

- Residue tolerances have been established for diuron in or on agricultural commodities that range from 0.1 to 7 ppm (U.S. EPA, 1985).

VII. ANALYTICAL METHODS

- Analysis of diuron is by a high-performance liquid chromatographic (HPLC) method applicable to the determination of certain carbamate and urea pesticides in water samples (U.S. EPA, 1986c). This method requires a solvent extraction of approximately 1 L of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and concentrated to a volume of 10 mL or less. HPLC is used to permit the separation of compounds, and measurement is conducted with an ultraviolet (UV) detector. The method detection limit has not been determined for diuron, but it is estimated that the detection limits for analytes included in this method are in the range of 1 to 5 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) and powdered activated carbon (PAC) adsorption and chlorination effectively remove diuron from water.

- El-Dib and Aly (1977b) determined experimentally the Freundlich constants for diuron on GAC. Although the values do not suggest a strong adsorption affinity for activated carbon, diuron is better adsorbed than other phenylurea pesticides.

- El-Dib and Aly (1977b) calculated, based on laboratory tests, that 66 mg/L of PAC would be required to reduce diuron concentration by 98%, and 12 mg/L of PAC to reduce diuron concentration by 90%.

- Conventional water treatment techniques of coagulation with ferric sulfate, sedimentation and filtration proved to be only 20% effective in removing diuron from contaminated water (El-Dib and Aly, 1977a). Aluminum sulfate was reportedly less effective than ferric sulfate.

- Oxidation with chlorine for 30 minutes removed 70% of diuron at a pH 7. Under the same conditions, 80% of diuron was oxidized by chlorine dioxide (EL-Dib and Aly, 1977a). Chlorination, however, will produce several degradation products whose environmental toxic impact should

be evaluated prior to selection of oxidative chlorination for treatment of diuron-contaminated water.

- The treatment technologies cited above for the removal of diuron from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt diuron removal from water must be based on a case-by-case technical evaluation and an assessment of the economics involved.

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